Gender Dysphoria in Adolescents

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2010

document version
Publisher's PDF, also known as Version of record

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Summary and general discussion

Introduction

Adolescents with gender dysphoria were the focus of this thesis. These youth have received considerable Dutch media attention over the last decade. On television, numerous documentaries were shown and various youth programs devoted a broadcast to the subject. Full color magazines published articles and one daily paper has recurrently reported on some of the youth since 2003. The World Press Photo awarded the 2010 third prize in the 'stories' category to a series on one of the adolescents attending the Amsterdam gender identity clinic.

The current media attention to this topic, not only in the Netherlands but also in North America, has led to a rising awareness of young people with gender dysphoria. In May 2007, the VU university medical center initiated the first meeting of the Adolescent Gender Identity Research (AGIR) network where clinical and research protocols were discussed. The network has now expanded to ten gender identity clinics from Europe and North America and two more will join soon. Participants of AGIR note both an increase in the number of referrals, and a decrease in the age at which adolescents apply for gender reassignment.[162] Hence, the importance of increasing our understanding of gender dysphoria in adolescents and developing a model of care for these youth has been emphasized (e.g. de Vries[209], Zucker[210]).

The extent and type of psychiatric comorbidity deserve more attention as do the implications for treatment. Puberty suppression is now an element of clinical management of adolescents with a gender identity disorder (GID) at the AGIR clinics around the world. However, different views exist on the criteria for puberty suppression and no evaluative studies have been performed yet.[211] In this thesis we have analyzed mental health in gender dysphoric adolescents and evaluated clinical management encompassing puberty suppression. Three studies on psychological (dys)functioning and comorbid psychiatric disorders were conducted. Two follow-up studies were performed, one on puberty suppression only and one on gender reassignment preceded by puberty suppression. These studies are summarized below, followed by a general discussion and recommendations for clinical management.

Summary

There is increasing evidence that biological, psychological and social factors all play a role in typical gender identity development.[10] In contrast, our understanding of gender variant development and GID remains limited. In **chapter two,** we present a review of studies on the psychosexual outcome in individuals with disorders of sex development (DSD) which provides some insight into the complex relationship between biological and psychosocial factors. A high percentage of affected individuals in these studies did suffer from gender dysphoria. However, these percentages varied substantially among the different DSD groups, ranging from 0 to 67%, indicating that many individuals with DSD exhibit no gender identity problems. Clearly, a distinction should be made between gender *role* behavior and gender *identity.* Whereas there are empirical findings suggesting that biological factors, especially prenatal sex hormones, influence the development of gender *role* behavior, there is less evidence that biological factors affect gender *identity* development.[8,9] Hence, the findings suggest that both biological and psychosocial factors play a role in gender variant development similar to the role they play in typical gender identity development. In addition, the studies on individuals with DSD indicate that patients who chose to make a gender change often did so in adolescence or young adulthood.[38]

In **chapter three** psychological (dys)functioning of adolescents with GID was compared to that of adults with GID. Age adapted versions of the same instrument, the Minnesota Multiphasic Personality Inventory (MMPI-2 or MMPI-A, respectively) were administered to adults and adolescents eligible for medical intervention (cross-sex hormones and puberty suppression, respectively). Most notable, psychological functioning of adolescents was more favorable compared to adults. Whereas 73% of the adults showed problem behavior in the clinical range on two or more clinical scales, in the adolescents this was only 32%. Further findings were that, contrary to what is found in some studies (for a review, see Lawrence[39], Murad[185]) no differences in psychological functioning were found in the adult transsexuals with regard to sexual orientation (sexually attracted to natal or non-natal gender). All adolescents were sexually attracted to their natal gender. Gender differences emerged as well: adult female-to-males (FtMs) functioned significantly better than adult male-to-females (MtFs) on three clinical scales. However, adolescent FtMs functioned significantly better than adolescent MtFs on only one clinical scale and the reverse was true on two clinical scales.

The salient finding in this study was the poorer psychological functioning of adult applicants for sex reassignment compared to adolescent applicants. This may reflect a better psychological functioning of early-onset GID as opposed to late-onset (after puberty) GID.[39,126] However, it also suggests that it is easier to make a gender role change around the start of puberty than in adulthood.

In **chapter four** the co-occurrence of autism spectrum disorders (ASD) and GID was examined in children and adolescents (115 boys and 89 girls, mean age 10.8) referred to a gender identity clinic. During the standardized assessment, a GID diagnosis was made and suspected ASD cases were identified. The Dutch version of the Diagnostic Interview for Social and Communication Disorders (10th rev., DISCO-10) was administered to ascertain ASD classifications. The incidence of ASD in the combined sample of children and adolescents was 7.8% (n=16), in the 108 assessed children 6.4% (*n*=7) and in the 96 assessed adolescents 9.4% (*n*=9). The incidence of ASD was higher in in children and adolescents with a GID-NOS (gender identity disorder not otherwise specified) diagnosis than in youth fulfilling the complete GID criteria (in children 6.5% (*n*=5) versus 1.9% (*n*=1) and in adolescents 37.5% (*n*=3) versus 13% (*n*=6) respectively). The mean IQ of the children with ASD (M=82.0) was significantly lower compared to the mean IQ of the children without ASD (M=103.9). Adolescents with ASD (M=15.4 years) were significantly older than adolescents without ASD (M=13.8 years).

The observed incidence of 7.8% ASD in the combined sample of 204 children and adolescents referred to a gender identity clinic is approximately ten times higher than the prevalence of 0.6%–1% of ASD in the general population.[142,143] This confirms the clinical impression that ASD occurs more frequently in gender dysphoric individuals than expected by chance. The cases described in the current study illustrate the clinical management issues that arise in youth with co-occurring GID and ASD. In all, the diagnostic procedure was extended to disentangle whether the gender dysphoria evolved from a general feeling of being 'different' or a 'core' cross-gender identity. Concerning gender reassignment, ASD does not have to be a strict exclusion criterion. However, to provide individuals with co-occurring gender dysphoria and ASD with proper care remains a challenge.

In **chapter five**, a study on psychiatric comorbidity in adolescents with GID was presented. To ascertain DSM-IV diagnoses, the Diagnostic Interview Schedule for Children (DISC) was administered to parents of 105 gender dysphoric adolescents (mean age at assessment 14.6 years, 53 natal males and 52 natal females). Of the 105 adolescents, 32.4% had at least one concurrent psychiatric disorder, and 15.2% had two or more comorbid diagnoses. Anxiety disorders occurred in 21%, mood disorders in 12.4% and disruptive disorders in 11.4% of the adolescents. Compared with natal females, natal males suffered more often from mood disorders (20.8% versus 3.8%) and social anxiety disorder (15.1% versus 3.8%). Adolescents were divided into an *immediately eligible* group, when the diagnostic procedure took less than 1.5 years and a *delayed eligible* group, when their diagnostic procedure took 1.5 years or more. The rate for oppositional defiant disorder and the rate for three or more comorbid diagnoses was higher in delayed eligible adolescents with GID (15.4% versus 3.2% and 7.4% versus 0%, respectively) compared with immediately eligible adolescents, their age was older (15.6 years versus 14.1 years) and their intelligence was lower (TIQ=91.6 versus 99.2).

We concluded that the majority of gender dysphoric adolescents do not have co-occurring psychiatric problems, despite their increased suffering from the incongruence between experienced and assigned gender after puberty had started. However, subgroups of adolescents do show comorbid psychiatric problems. Natal males seem to need more clinical attention than natal females. Contrary to our expectation, psychiatric comorbidity by itself was only minimally associated with eligibility for medical interventions. Other factors, like age, intelligence and family circumstances, seem to be of importance too.

In **chapter six**, the effects of puberty suppression on psychological functioning and gender dysphoria were evaluated, shortly before cross-sex hormone treatment was initiated, in adolescents with GID who had received GnRHa to suppress puberty. The first 70 eligible candidates who received puberty suppression between 2000 and 2008 were assessed twice: at T0, when attending the gender identity clinic, before the start of GnRHa; and at T1, shortly before the start of cross-sex hormone treatment. Behavioral and emotional problems, depressive symptoms, anxiety and anger, general functioning, gender dysphoria and body satisfaction were assessed. Behavioral and emotional problems and depressive symptoms decreased whereas general functioning improved significantly during puberty suppression. Feelings of anxiety and anger did not change between T0 and T1. While changes over time were equal for both genders, compared with natal males, natal females were older when they started puberty suppression and showed more problem behavior at both T0 and T1.

By relieving the acute distress accompanying the gender dysphoria, puberty suppression seemed to have offered these youths the possibility of healthy psychological development.

Long term outcome of young adults after their gender reassignment surgery who had been treated with puberty suppression during adolescence was assessed in **chapter seven**. For this study, we investigated gender dysphoria, treatment satisfaction, current life situation and school or employment career, sexual functioning and quality of life. Twenty-seven young adults (11 FtMs and 16 MtFs) were assessed twice: first, shortly after their attendance at the gender identity clinic (pre-treatment, mean age 13.5 (SD 1.8)) and second, at least one year after their GRS (post-treatment, mean age 20.9 (SD 1.0)). Gender dysphoria resolved and participants were predominantly satisfied with their bodies and treatment. Concerning relationships with family and peers, and professional and educational careers, they had made important age appropriate developmental transitions. Although, compared to their peers in the general Dutch population, participants showed less experience with various sexual behaviors, the number of experiences had increased after gender reassignment surgery. Many young adults (78%) had been involved in romantic relationships. Quality of life appeared to be better compared with scores from 21-30 year old participants from a survey on the psychometric properties of

the WHOQOL-Bref.[187] Pre-treatment intelligence and poor peer relations correlated negatively with post-treatment quality of life. These findings suggest that clinical management including puberty suppression, enabled these formerly gender dysphoric adolescents to make important age appropriate developmental transitions, contributing to a satisfactory qualify of life. A subgroup of adolescents, however, showing a poorer quality of life post-treatment, deserves special clinical attention.

General discussion

Mental health

Comorbidity, the presence of two or more psychiatric disorders, occurs frequently among youth attending mental health services. It is of relevance to understand whether putative comorbid problems actually represent distinct disorders, whether shared or overlapping risk factors play a role, or whether one disorder creates an increased risk for another.[212] In persons with GID, there is a continuing debate as to whether associated psychopathology is a cause, a consequence or a random unrelated co-occurrence.[31]

In a substantial proportion of the gender dysphoric adolescents studied (68%) no comorbid psychopathology occurred and psychological functioning, measured (by means of the MMPI, the CBCL and the YSR) in adolescents eligible for medical interventions, was in the non-clinical range. Both categorical (whether someone has a specific psychiatric disorder or not) and continuous (the degree of problem behavior someone has) measures were used, with results pointing in the same direction.

Only a few other studies in adolescents with GID exist. Their results indicate more associated problem behavior, both internalizing and externalizing.[40,163] One explanation for the relatively favorable functioning of our adolescents is that early medical intervention was not offered yet in the other studies. At the Amsterdam gender identity clinic, adolescents may have felt that they would receive puberty suppression when needed. This trust has likely contributed to their mental health. In adult transsexuals, postoperative psychopathology is associated with difficulties in passing in their new gender.[136] Our study comparing adults and adolescents suggests that a gender role transition at an early age, supported by puberty suppression, is possibly easier and avoids later psychological problems. Significant is that, as a consequence of their young age, most adolescents came to our gender identity clinic with the support of their families. Those who were not supported probably needed to wait until adulthood before applying for treatment. The importance of social support was emphasized by a study in adults with GID. Suicidality and depression were related to gender-related abuse experienced across the life course, especially during adolescence.[135]

Still, gender dysphoric adolescents presenting with psychiatric comorbidity are of concern. The increased occurrence, compared with the general population,[173,174] of emotional disorders (anxiety disorders 21% and mood disorders 12%) and disruptive disorders (11.4%) indicates that many adolescents with GID are still in despair, despite their awareness of timely interventions. It may be deemed that being gender dysphoric is stressful. The 10% prevalence of social phobia suggests that the development of gender variant adolescents' peer relations is at stake in a non-negligible subgroup. Indeed, in a study comparing gender dysphoric children with adolescents, the latter showed poorer peer relations, which were in turn the strongest predictor of CBCL psychopathology.[40]

Special attention should be paid to the gender differences found in the various studies of this thesis, which did not always point in the same direction. There may be various explanations for these gender differences. In the psychiatric comorbidity study, natal males suffered more often from mood disorders and social anxiety disorder and from two or more diagnoses compared with natal females. In contrast, in the general population the rates of anxiety and depression are generally higher in female than male adolescents and the prevalence rate of disruptive disorders is lower in females compared to males.[173,174] Possibly, adolescents with GID not only show gender stereotyped behavior in the direction of the identified gender, but also show the associated problem behaviors typical for that gender.

When the effects of puberty suppression were evaluated, both genders improved over time, but FtMs showed more externalizing problem behavior, trait anger and trait anxiety compared with MtFs both at baseline and at evaluation. An explanation might be that in most natal females puberty had already started and they had developed breasts and had their menarche. Because it is less perceivable for the environment, some puberty development in FtMs (e.g. menstruation) is sometimes considered not as dramatic as beard growth or breaking of the voice in MtFs. However, the higher problem scores of FtMs may indicate that this assumption is erroneous. This was also reflected in the MMPI study: 22.5% of the adolescent FtMs scored in the clinical range on the Social Introversion scale (measures whether someone is comfortable with other people), whereas this was only 4.7% in adolescent MtFs. Future studies should further examine gender differences in psychological (dys)functioning in adolescents with GID.

The ten-fold higher incidence of ASD in adolescents referred to a gender identity clinic compared to the general population,[142] has not only clinical, but also theoretical implications. Theoretically, it can be assumed that ASD creates an increased risk for developing GID, which will then be diagnosed as a distinct disorder. For example, it may be that individuals with ASD have difficulty developing more flexible thinking around gender stereotypes. While rigid gender stereotyped thinking occurs in typical gender development in young children,[158] they become more flexible after their preschool years. Youth with ASD might not or not fully reach that stage of flexible thinking. Another

putative shared factor postulated in both the vulnerability of ASD and GID is the role of prenatal testosterone. Studies in girls with congenital adrenal hyperplasia, who are prenatally exposed to high levels of testosterone, showed that they had more traits of ASD than controls and some developed gender identity problems.[80,213] However, co-occurring gender dysphoria and ASD in natal males remains unexplained by the prenatal androgen exposure hypothesis.

Treatment evaluation

There is now some preliminary evidence to conclude cautiously that the so-called 'Dutch protocol', adopted by other gender identity clinics around the world, meets its expectations. The improvement in psychological functioning and the remittance of gender dysphoria are in line with many studies in adults that show that psychological functioning and quality of life improve and that gender dysphoria is alleviated after gender reassignment (for a review, see Murad[185]). Medical interventions for gender dysphoric adolescents including puberty suppression as part of an extended diagnostic phase may provide a valuable component of clinical management.

A reason for the positive treatment outcome in the studied adolescents may be that, in the Netherlands, social and school environments often show a relatively high level of tolerance to and support of gender variant behavior. In cross-cultural studies, the Netherlands emerged as a country with the most accepting attitude with respect to homosexuality and the least homophobia.[200,201] Relevant in this respect are also studies on psychological functioning of two other large gender identity clinics for children and adolescents, in Toronto and London. Their reports on comorbid problematic behavior in gender dysphoric adolescents are more worrisome, with much higher rates of co-occurring problematic behavior.[40,163,166]

That gender dysphoric adolescents may profit from medical interventions was also concluded in the recently developed clinical guidelines on Endocrine Treatment of Transsexual Persons.[4] In that document the requirement in the standards of care (SOC[5]) developed by the World Professional Association of Transgender Health (WPATH) that puberty should have progressed at least to Tanner stage 2 was adopted. With the upcoming seventh version of WPATH's SOC, it seems reasonable not to change this criterion. It is not possible to distinguish during childhood between children in whom gender dysphoria will remit and those in whom it will remain.[34] Therefore, the advice not to make a complete gender role change is sensible in prepubertal children with GID. The distinction between GID in childhood and GID in adolescence/adulthood is also reflected in the DSM-IV-TR criteria[2] and in the proposed criteria of the DSM-5, with different sets of criteria for children and adolescents/adults, respectively.[29,30]

The results of this thesis are promising and of importance in understanding gender dysphoria in adolescents, but should be interpreted in the light of several limitations and the need for further research.

First, these follow-up studies of adolescents who had received puberty suppression come from only one clinic and the results presented need to be replicated in other clinics. Some cross-national studies on gender dysphoric children do exist[41,214,215], but studies on adolescents attending gender identity clinics are completely lacking. Cross-national and cross-clinic collaborative studies should be developed. Recently, this has been decided upon by clinics collaborating in the AGIR network. We expect this to lead to new useful information in this field.

Some factors might have influenced the outcome of the evaluation studies in this thesis. As the adolescents in these studies were the first group receiving puberty suppression, both clinicians and parents were extremely cautious in considering whether the required eligibility criteria (a diagnosis of GID, persistent gender dysphoria since childhood, living in a supportive environment, no serious comorbid psychiatric disorders or other factors interfering with the diagnostic assessment, see Cohen-Kettenis[50]) were fulfilled. For example, the mean age at start of GnRHa analogs was 14.75 years, which is already after the start of puberty in typical developing children. Hence, the majority of the adolescents, especially the FtMs, had developed puberty stages further than Tanner 2–3 (which is the first stage of puberty), and can be considered as 'late' starters (unpublished results). Future studies should incorporate and focus specifically on the effects of an 'early' start of puberty suppression, that is before Tanner stage 4–5 (which is the last stage of puberty), as these 'early' starters are underrepresented in the current studies.

In addition, puberty suppression and gender reassignment should also be evaluated in adolescents with psychiatric comorbidity and other co-occurring problems that result in 'delayed eligibility' for medical interventions. In the current outcome studies, these groups were also underrepresented, as the eligibility criteria formulated were very strict for this first group of applicants for puberty suppression. For example, adolescents with co-occurring ASD and GID who were considered eligible for gender reassignment were not yet evaluated after gender reassignment surgery.

Further, this study was a longitudinal observational descriptive cohort study. A blinded randomized controlled trial design is for obvious reasons not possible. It is also highly unlikely that adolescents would be motivated to participate. Moreover, disallowing puberty suppression, resulting in irreversible development of secondary sex characteristics may be considered unethical.[186] It has been suggested that adolescents attending gender identity clinics in different countries which adhere to different treatment policies (GnRHa treatment at Tanner stage 2 versus Tanner stage 4/5) be compared. A difficulty in

carrying out such a study, however, is that cultural factors (as mentioned before) have an impact on the well being of gender dysphoric adolescents. Consequently, different treatment protocols as well as different cultures would be compared. Still, cross-cultural, cross-clinic collaborative studies may prove to be an efficient way to gather missing information.

Clearly, the co-occurrence of GID and ASD needs future research. The study in this thesis was performed on children and adolescents referred to the Amsterdam gender identity clinic. Whether other clinics have the same high ASD occurrence remains to be replicated. No studies have been published on ASD in adults with GID, despite the numerous studies on psychiatric comorbidity in adult transsexuals (for a review, see Murad[185]), and despite the frequent clinically reported occurrence of individuals suspected as having ASD who present themselves at adult gender identity clinics. Although all but one published case reports describe children and adolescents[145-147,150], it is conceivable that the co-occurrence exists in adults as well.

No definite results exist yet on the effects of GnRHa treatment to suppress puberty on physical and brain development. Although no serious side effects are reported in much larger non-GID patient groups (in children with precocious puberty and in reproductive medicine, see for example Shalev[176]), the effects of suppressing puberty in gender dysphoric adolescents have to be evaluated. Puberty is, for example, specifically important for bone mineral density development and the absence of sex hormones may be of influence on blood lipids and glucose metabolism. The first study on bone density development of gender dysphoric adolescents treated with GnRHa are favorable in this respect, showing that although mineral bone density decreases while puberty is suppressed, it catches up as soon as cross-sex hormones are introduced.[216] Also, with regard to adolescents' insulin sensitivity, no serious GnRHa side effects were detected.[217] One case-study presents a formerly gender dysphoric 33 year old transman whose puberty had been suppressed during adolescence, who is functioning well both physically and psychosocially.[218] With regard to brain development, fMRI studies are currently being performed to show the effects of GnRH analogs and cross-sex hormone treatment.

Finally, no long-term effects of the intervention with GnRHa exist yet. In chapter seven, young adults at least one year after their gender reassignment surgery had made many age appropriate developmental transitions with regard to their school or employment careers and sexual functioning. Most of them were satisfied with their lives. However, long-term follow up studies of former gender dysphoric adolescents in their later adulthood are needed. Further studies should be carried out on their psychosocial functioning, in terms of professional careers, long-term relationships, family life and if they have specific needs to function well in general.

Clinical implications

It should be noted that all adolescents with a GID diagnosis in our study were considered eligible for puberty suppression and were deemed to profit from gender reassignment: those with and without psychiatric comorbidity (including ASD) and scoring in the clinical range or below. Nevertheless, we found that it was relevant to distinguish between adolescents who were considered immediately versus those considered delayed eligible for medical interventions.

The relatively large group of well-functioning adolescents with no comorbid psychosocial problems, often considered immediately eligible for puberty suppression, needs only a careful assessment. Part of this group already presented themselves in childhood at the gender identity clinic, so clinicians know them well. Some may profit from some sort of psychosocial support, as their gender role transition and their social position may give rise to stress and reactive emotional problems, such as social anxiety. Also, in clinical practice, we often encounter young adolescents who have difficulty expressing themselves verbally about their gender dysphoric feelings. A sort of non-verbal psychotherapy may then be very useful (for example psychomotor therapy). Nevertheless, in general, it is clear that the well-functioning adolescents not only profit from puberty suppression and gender reassignment, but are also able to function adequately and adapt well to different life events, including gender role transition.

More than usual clinical attention is needed for the smaller, but more complex, often delayed eligible group of adolescents with comorbid psychiatric and social problems. Although they may also profit from medical interventions, their diagnostic assessment procedure is always lengthy (often more than one and a half years) and is accompanied by intensive psychotherapy or other psychological interventions. Gender dysphoria is rare in adolescence and therefore only one clinic is providing specialized care in the Netherlands. In this regard it is important that there are other mental health professionals and clinics spread out over the Netherlands with enough knowledge and willingness to collaborate with the Amsterdam gender identity clinic to provide gender dysphoric adolescents with comorbid problem behavior with appropriate care.

Both groups needed considerable clinical attention before a GID diagnosis and eligibility decision were made, with a mean duration of the assessment of almost 10 monthly sessions in the immediately eligible group and up to four years in the delayed eligible group. In the former group it might be considered, whether a shorter assessment procedure can be achieved. As a substantial part of the adolescents had psychiatric comorbidity and almost 10% suffered from ASD, a psychiatric evaluation, that is part of the standard assessment, proved its usefulness and should remain incorporated.

Although the protocol worked well for most adolescents in the current study, two groups need specific attention: FtMs who were in puberty already below the age of

12 years, and MtFs between the age of 12 and 16 in whom growth in height continued. For these groups the strict age criteria of 12 years for puberty suppression and 16 years for cross-sex hormone treatment should, in individual cases, be reconsidered.

A specific group comprises adolescents with co-occurring GID and ASD. For clinical care, it is important that clinicians at gender identity clinics do in fact diagnose a comorbid ASD when it occurs and know how to manage this co-occurrence. Collaboration with an ASD clinic can be advantageous and specialized training to recognize and treat individuals with ASD is warranted. Ideally, gender identity clinics should have the necessary resources to provide specialized ASD care as well, especially because individuals with concurrent GID and ASD can also be eligible for GR and profit from it.

Finally, it is probably not only the 'Dutch protocol' that is responsible for the encouraging results of these studies, but various aspects specific to the Dutch situation as well. In other countries, care for individuals with GID is often scattered, making easy communication about the adolescents in the gender reassignment process difficult. The Amsterdam gender identity clinic, however, provides multidisciplinary (psychological, psychiatric, medical and surgical) care for gender dysphoric children, adolescents and adults. The clinic has weekly patient sessions. If adolescents function problematically, physicians, psychologists and psychiatrists have the opportunity to quickly inform each other and act upon the information. Further, the tolerance and social and financial support (gender reassignment is covered by health insurance) of gender dysphoric individuals in the Netherlands may have contributed to the favorable outcome of the adolescents in this study.

We realize that, apart from medical interventions, family, friends, support groups, media and other advocates of gender variant behavior all have their share in the well-being of adolescents with GID. The rising awareness in the general population that young people may suffer from gender dysphoria has helped many adolescents to find their way to our clinic and has resulted in a better acceptance of gender dysphoric youth.